THESIS ABSTRACT

Stearylamine-Bearing Cationic Liposome For Targeted Anti-Cancer Therapy And Its Role In Immunomodulation

Cancer is the leading cause of death worldwide. Potential toxicity and many side effects of chemotherapeutics can mainly be explained by a lack of adequate specificity for tumor cells. It has been found that living tumor cells and endothelial cells of the tumor blood vessels express phosphatidylserine (PS) on their surface. Thus PS may be an attractive target for the tumor blood vessels as well as the living tumor cells. Herein we report for the first time that cationic liposome composed of phosphatidylcholine (PC) and stearylamine (SA) selectively kills some cancer cells. This killing activity correlates with the membrane exposure of negatively charged PS on the surface of these cells and the capacity of the cationic liposome to intercalate with PS. Most strikingly, non cancerous cells were only marginally affected even at the highest dose of liposome due to extremely low surface PS content. Here, we explored the target selectivity mechanisms of PC-SA liposomes that result in cell growth arrest and apoptosis of cancer cells, showcasing features like binding to annexin V, dissipation of mitochondrial membrane potential, increased level of reactive oxygen species (ROS), appearance of apoptotic nuclei by cell cycle analysis and involvement of p-ERK, cleaved PARP, cleaved caspases, cytochrome *c* release, and p-PI3K. Combination therapy with doxorubicin and camptothecin in these vesicles demonstrated a manyfold enhancement in the efficacies of these anti-cancer drugs both *in vitro* and across different advanced tumor models without any signs of toxicity. Besides having better killing activity, doxorubicin in SA liposomes, maintained the anti-tumor immune response of free liposome and free drug on $CD4^+$ and $CD8^+$ T cells for Th1 cytokines production. This unique mode of selectivity towards PS of cancer indicates that the SA-bearing liposomes might be valuable as delivery system as well as therapy against and cancers which have elevated surface levels of negatively charged phospholipid (PS), in addition maintaining and augmenting the beneficial immunomodulatory activities of free drug toward T cells.

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